WHAT IS CLAIMED IS:

1. An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered PYI motif at residues 564-566.

2. The isolated polypeptide of claim 1, wherein residues 564-566 are replaced by DDD.

3. The isolated polypeptide of claim 1, wherein residues 564-566 are replaced by AAA.

4. An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered P564 residue.

5. The isolated polypeptide of claim 4, wherein residue 564 is replaced by A.

6. The isolated polypeptide of claim 4, wherein residue 564 is replaced by H.

7. An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered YI656-566 residue.

8. An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered PM567-568 residue.

9. An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered DDD569-571 residue.

10. An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered K547 residue.

11. The isolated polypeptide of claim 10, wherein the amino acid at position 547 is replaced by R.

12. An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered Y565 residue.

13. The isolated polypeptide of claim 12, wherein the amino acid at position 565 is replaced by G.

14. An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered I566 residue.

15. The isolated polypeptide of claim 14, wherein the amino acid at position 566 is replaced by G.

16. An isolated polypeptide comprising an amino acid of SEQ ID NO:4 and fragments thereof with an altered FQL 572-574 residue.

17. The isolated polypeptide of claim 16, wherein the amino acids at positions 572-574 are replaced by AQA.

18. An isolated nucleic acid molecule comprising a polynucleotide sequence which encodes the polypeptide of claim 1.

19. A vector comprising the nucleic acid molecule of claim 18 in operative association with at least one promoter.

20. A host cell transformed or transfected with the vector of claim 19.

21. A pharmaceutical composition comprising the isolated polypeptide of claim 1 and at least one pharmaceutical carrier or adjuvant.

22. The vector of claim 19, wherein the vector is a

plasmid.

23. The vector of claim 19, wherein the vector is a viral vector.

24. The vector of claim 19, wherein the vector is a retroviral vector.

25. The host cell of claim 20, wherein the host cell is a prokaryotic cell.

26. The host cell of claim 25, wherein the host cell is a bacterial cell.

27. The host cell of claim 25, wherein the host cell is a eukaryotic cell.

28. The host cell of claim 25, wherein the host cell is a mammalian cell.

29. A method of making a protein or a functional fragment thereof, comprising:

introducing a nucleic acid according to claim 18 into a host cell or cellular extract;

incubating said host cell or cellular extract under conditions such that said nucleic acid is expressed as a

transcript and said transcript is expressed as a translation product comprising said protein; and

isolating said translation product.

30. An isolated protein or a functional fragment thereof made by the method of claim 29.

31. A method of producing an isolated degradation box protein, comprising:

infecting, transforming, or transducing a host cell with an expression vector comprising the nucleic acid of SEQ ID NO:2;

culturing said host cell; and

removing the isolated protein from said host cell.

32. An isolated protein or a functional fragment thereof, made by the method of claim 31.

33. A method of screening for an agent which modulates N-TAD function, comprising:

incubating a mixture comprising:

an isolated protein according to claim 29;

a target protein; and

a candidate agent

under conditions whereby, but for the presence of said agent, said isolated protein specifically

transactivates reporter genes, or mediates VHL-dependent degradation, or physically interacts with VHL at a reference affinity;

detecting the binding affinity of said isolated protein to said target protein to determine an agent-biased affinity;

wherein a difference between said reference affinity and said agent-biased affinity indicates that said agent modulates the functional activity of said isolated protein to said target protein.

34. The method of claim 33 wherein the target protein is VHL or a fragment thereof.

35. The method of claim 33 wherein the incubation is at normoxia.

36. The method of claim 33 wherein the incubation is at hypoxia.

37. A method of evaluating a potential analog of the PYI motif or P564 spanning protein or a functional fragment thereof for VHL-HIF-1 alpha interaction modulating efficacy, comprising:

determining a natural VHL-HIF-1 alpha interaction within a cell, a group of cells, or an organism;

administering said potential analog to an equivalent test cell, group of cells, or organism;

measuring the level of VHL-HIF-1 alpha interaction in said test cell, group of cells, or organism; and

determining said potential analog is efficacious when the measured test level of VHL-HIF-1 alpha interaction is equal to or greater than the natural level of VHL-HIF-1 alpha interaction.

38. The method of claim 37, wherein said test cell, group of cells, or organism are at normoxia.

39. The method of claim 37 wherein said test cell, group of cells, or organism are at hypoxia.

40. A method of evaluating an antagonist of the PYI motif or P564 spanning protein or a functional fragment thereof for VHL-HIF-1 alpha interaction inhibiting efficacy, comprising:

determining a normal level of VHL-HIF-1 alpha interaction in a cell, a group of cells, or an organism;

administering said antagonist to an equivalent test cell, a group of cells, or an organism;

measuring the level of VHL-HIF-1 alpha interaction in said test cell, group of cells, or organism; and

determining said antagonist is efficacious when the

measured test level of VHL-HIF-1 alpha interaction is less than the normal level of VHL-HIF-1 alpha interaction.

41. The method of claim 40, wherein said test cell, group of cells, or organism are at normoxia.

42. The method of claim 40, wherein said test cell, group of cells, or organism are at hypoxia.

43. A method of regulating the HIF-1 alpha signaling pathway of a bioentity selected from the group consisting of a cell, group of cells and a living organism, comprising administering a substance selected from the group consisting of a PYI motif, a functional fragment of a PYI motif, an analog of a PYI motif, a P564 spanning protein, a functional fragment of a P564 spanning protein, and an analog of a P564 spanning protein to said cell, group of cells, or living organism.

44. A method of regulating the HIF-1 alpha signaling pathway of a bioentity selected from the group consisting of a cell, group of cells and a living organism, comprising administering an antagonist of a PYI motif or an antagonist of a P564 spanning protein to said cell, group of cells, or living organism.

45. A method of treating disease, comprising administering full length HIF-1 alpha or an analog thereof, said full length HIF-1 alpha or analog containing at least one mutation or modification of the PYI motif to a cell, a group of cells, or an organism.

46. The method of claim 45 wherein said disease is an ischemic condition.

47. The method of claim 46 wherein said ischemic condition is selected from the group consisting of: brain infarction, heart infarction, and circulatory disorder.

48. A method of treating a disease selected from the group consisting of cancer, hypertension, demyelinating disorders, diffuse proliferative glomerulonephritis, toxoplasmosis caused retinochorioidits, HIV caused Tat angiongenesis, HIV caused Kaposi's sarcoma, hepatitis caused inflammation, hepatitis caused angiogenesis, chronic ulceration, proliferative retinopathy, retina hemangioblastomas, neovascularization, arterial hypervascularization, sarcoidosis, bullous skin disease, vasculitis with angiogenesis, dermatomyositis with angiogenesis, polymyositis with angiogenesis rheumatoid arthritis,

juvenile osteoarthritis, polyarthritis, aneurysm and atheroma, comprising administering an antagonist of the PYI motif or P564 spanning protein or a functional fragment thereof to a cell, a group of cells, or an organism.

49. A method of treating disease, comprising administering an agonist of the PYI motif or P564 spanning protein or a functional fragment thereof to a cell, a group of cells, or an organism.

50. The method of claim 49, wherein said disease is selected from the group consisting of ischemia, brain infarction, heart infarction, and circulatory disorder.

51. A method of promoting conditions in an *in vitro* culture, comprising adding a substance selected from the group consisting of a constitutively active HIF-1 alpha mutant, a functional fragment of a constitutively active HIF-1 alpha mutant, an agonist of the PYI motif, and an agonist of the P564 spanning protein to the culture.

52. The method of claim 51 wherein the culture is used to sustain or grow neural stem cells.

53. A pharmaceutical composition comprising a

substance selected from the group consisting of a PYI motif, a functional fragment of the PYI motif, an analog of the PYI motif, a P564 spanning protein and a functional fragment of a P564 spanning protein, and an analog of a P564 spanning protein, and at least one pharmaceutical carrier or adjuvant.

54. A pharmaceutical composition comprising an antagonist of the PYI motif or an antagonist of the P564 spanning protein, and at least one pharmaceutical carrier or adjuvant.

55. A method of regulating the function of a molecule selected from the group consisting of HIF-1 alpha, EPAS, and HIF-3alpha in a cell, a group of cells, or an organism, comprising administering to said cell, group of cells, or organism a substance selected from the group consisting of the PYI motif, a functional fragment of the PYI motif, an analog of the PYI motif, a P564 spanning protein, a functional fragment of a P564 spanning protein, and an analog of a P564 spanning protein to said cell, group of cells, or organism.

56. A method of regulating the function of a molecule selected from the group consisting of HIF-1 alpha, EPAS, and HIF-3alpha in a cell, a group of cells,

or an organism, comprising administering an antagonist to the PYI motif or an antagonist to the P564 spanning protein to said cell, group of cells, or organism.

57. A method of effecting degradation of a molecule selected from the group consisting of HIF-1 alpha, EPAS, and HIF-3alpha in a cell, a group of cells, or an organism, comprising administering a substance selected from the group consisting of the PYI motif, a functional fragment of the PYI motif, an analog of the PYI motif, a P564 spanning protein, a functional fragment of a P564 spanning protein, and an analog of a P564 spanning protein to said cell, group of cells, or organism.

58. A method of increasing angiogenesis, comprising administering a HIF-1 alpha mutant having an alteration of at least one residue selected from the group consisting of K547, P564, Y565, I566, D569, D570, and D571 to a cell, a group of cells, or an organism.

59. A method of regulating angiogenesis, comprising administering a HIF-1 alpha mutant having an alteration of at least one residue selected from the group consisting of K547, P564, Y565, I566, D569, D570, and D571 to a cell, a group of cells, or an organism.

60. A method of increasing erythropoiesis, comprising administering a HIF-1 alpha mutant having an alteration of at least one residue selected from the group consisting of K547, P564, Y565, I566, D569, D570, and D571 to a cell, a group of cells, or an organism.

61. A method of regulating erythropoiesis, comprising administering a HIF-1 alpha mutant having an alteration of at least one residue selected from the group consisting of K547, P564, Y565, I566, D569, D570, and D571 to a cell, a group of cells, or an organism.

62. A method of controlling oxygen-dependent degradation of a protein, comprising incorporating the sequence of SEQ ID NO:5 in a cellular protein.

63. The method of claim 62 wherein said protein is GAL-4.

64. A method of detecting an HIF-1 alpha sequence encoding an oxygen-independent degradable HIF-1 alpha mutant, comprising evaluating of a sample sequence for an alteration to any one of residues 532 through 585.

65. The method of claim 64, wherein said alteration occurs to a residues selected from the group consisting

of K547, P564, Y565, I566, P567, M568, D569, D570, D571, F572, Q573 and L574.

66. The method of claim 64, wherein said evaluation is effected by means selected from the group consisting of oligonucleotide probes, PCR-based diagnosis and antibodies.